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EXAMINER	**DATE CONSIDERED**

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with **MPEP 609**; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

PATENT APPLICATION SERIAL NO._____

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01 FC:1011 310.00 DA
02 FC:1111 510.00 DA
03 FC:1311 210.00 DA
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PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number: 12229074

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	$155		N/A	$310
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	$255		N/A	$510
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	$105		N/A	$210
TOTAL CLAIMS (37 CFR 1.16(i))	34 minus 20 =	* 14	X $25 =		OR	X $50 =	700
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	* 0	X $105 =			X $210 =	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).		$130			$260	
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			$185			$370	
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1736

APPLICATION AS AMENDED – PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDI-TIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDI-TIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $25 =		OR	X $50 =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $105 =		OR	X $210 =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					$185		OR	$370	
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDI-TIONAL FEE ($)	OR	RATE ($)	ADDI-TIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $25 =		OR	X $50 =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $105 =		OR	X $210 =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					$185		OR	$370	
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Express Mail No.: EV654846492US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Jerome B. Zeldis

Application No.: To Be Assigned
(Divisional of Serial No. 10/438,213)

Filed: August 19, 2008

For: METHOD FOR TREATING MULTIPLE MYELOMA USING 4-(AMINO)-2-(2,6-DIOXO(3-PIPERIDYL))-ISOINDOLINE-1,3-DIONE (as amended)

Confirmation No.: To Be Assigned

Group Art Unit: To Be Assigned

Examiner: To Be Assigned

Attorney Docket No.: 9516-773-999
(CAM: 501872-999773)

INFORMATION DISCLOSURE
STATEMENT UNDER 37 C.F.R. §1.56 AND §1.97

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the continuing duty of disclosure imposed by 37 C.F.R. § 1.56 and § 1.97 to inform the Patent Office of all references coming to the attention of each individual associated with the filing or prosecution of the subject application, which are or may be material to the patentability of any claim of the application, Attorneys for Applicants hereby invite the Examiner's attention to references **A01** to **A82, B01** to **B08,** and **C01** to **C204** listed on the attached revised form PTO 1449 entitled "List of References Cited by Applicant." The above-identified application is a divisional of prior U.S. Application No. 10/438,213, filed May 15, 2003. Copies of references **A01** to **A82, B01** to **B08,** and **C01** to **C204** are not provided herewith; rather, pursuant to 37 C.F.R. § 1.98(d), Applicants respectfully invite the Examiner's attention to the file of parent application Serial No. 10/438,213, filed May 15, 2003, since these references were made of record in the prosecution of the parent applications.

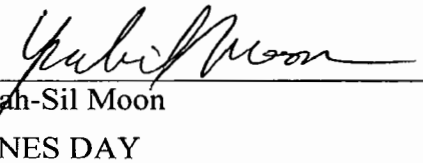
Identification of the listed references is not meant to be construed as an admission of Applicants or Attorneys for Applicants that such references are available as "prior art" against the subject application.

Applicants respectfully request that the Examiner review the foregoing reference and that the reference be made of record in the file history of the application.

Pursuant to 37 C.F.R. § 1.97(b), Applicants estimate that no fee is due in connection with the filing of this Information Disclosure Statement. However, should the Patent Office determine otherwise, please charge the necessary fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: August 19, 2008



52,042

Yeah-Sil Moon (Reg. No.)

JONES DAY
222 East 41st Street
New York, New York 10017-6702
(212) 326-3939

Enclosure

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/229,074	Filing Date 08/19/2008	☐ To be Mailed

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	08/19/2008	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 35	Minus	** 35	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/KATRINA S. TURNER/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

JONES DAY DOCKET NO. 9516-773-999

Express Mail No. EV654846492US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Prior application: Examiner Chris E. Simmons

Art Unit 1614

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is a request for filing a ☐ continuation ☒ divisional application under 37 CFR § 1.53(b), of pending prior application no. 10/438,213 filed on May 15, 2003.

of Jerome B. Zeldis

(inventor(s) currently of record in prior application)

for METHOD FOR TREATING MULTIPLE MYELOMA USING 4-(AMINO)-2-(2,6-DIOXO(3-PIPERIDYL))-ISOINDOLINE-1,3-DIONE (as amended)

(title of invention)

1. ☒ The filing fee is calculated below:

PATENT APPLICATION FEE VALUE

TYPE	NO. FILED	LESS	EXTRA RATE		FEE
Total Claims	35	- 20	15	$50.00 each	$ 750.00
Independent	2	- 3	0	$200.00 each	$ 0.00
Total Number of Pages w/ drawings (excluding electronically filed sequence or computer code listing)	59	-100	0	$250.00 for each 50 pages over 100	$ 0.00
				Basic Filing Fee ($310.00)	$ 310.00
				Examination Fee ($210.00)	$ 210.00
				Search Fee ($510.00)	$ 510.00
				Multiple Dependency Fee If Applicable ($370.00)	$
				Total	$ 1780.00
				Applicant qualifies for the 50% Reduction for Independent Inventor, Nonprofit Organization or Small Business Concern.	$ 0.00
				Applicant qualifies for an additional $75.00 reduction in Basic Filing Fee for Independent Inventor, Nonprofit Organization or Small Business Concern Filing Electronically.	.00
				Total Filing Fee	$ 1780.00

09/12/2008 MNGUYEN 00000025 503013 12229074

01 FC:1202 50.00 DA

2. ☒ The above calculation is an estimate of the fees due. Please charge the required fees to Jones Day Deposit Account No. 50-3013. A copy of this sheet is enclosed.

NYI-4113883v1

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/229,074	08/19/2008	1612	1780	9516-773-999	35	2

CONFIRMATION NO. 7450

20583
JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

FILING RECEIPT

OC000000032059496

Date Mailed: 09/16/2008

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Jerome B. Zeldis, Princeton, NJ;

Assignment For Published Patent Application

Celgene Corporation

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a DIV of 10/438,213 05/15/2003
which claims benefit of 60/380,842 05/17/2002
and claims benefit of 60/424,600 11/06/2002

Foreign Applications

If Required, Foreign Filing License Granted: 09/12/2008

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/229,074**

Projected Publication Date: 12/25/2008

Non-Publication Request: No

Early Publication Request: No

Title

Methods for treating multiple myeloma using 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3dione

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/229,074	08/19/2008	Jerome B. Zeldis	9516-773-999

CONFIRMATION NO. 7450

20583
JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

PUBLICATION NOTICE

OC000000033803749

Title: Methods for treating multiple myeloma using 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3dione

Publication No.US-2008-0317708-A1
Publication Date:12/25/2008

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

ELECTRONIC FILING

PTO/SB/96 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner:	Celgene Corporation		
Application No./Patent No.:	12/229,074	Filed/Issue Date:	August 19, 2008
Entitled:	METHOD FOR TREATING MULTIPLE MYELOMA USING 4-(AMINO)-2-(2,6-DIOXO(3-PIPERIDYL))-ISOINDOLINE-1,3-DIONE (AS AMENDED)		

Celgene Corporation , a corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☒ the assignee of the entire right, title, and interest; or
2. ☐ an assignee of less than the entire right, title and interest. The extent (by percentage) of its ownership interest is %

in the patent application/patent identified above by virtue of either:

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 021461, Frame 0407, or for which a copy thereof is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

1. From: To:
The document was recorded in the United States Patent and Trademark Office at Reel , Frame , or for which a copy thereof is attached.

2. From: To:
The document was recorded in the United States Patent and Trademark Office at Reel , Frame or for which a copy thereof is attached.

3. From: To:
The document was recorded in the United States Patent and Trademark Office at Reel , Frame , or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

☐ Copies of assignments or other documents in the chain of title are attached.

[NOTE: A separate copy (*i.e.*, the original assignment document or a true copy of the original document) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 02.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Yeahsil Moon	12/10/2009
Signature	**Date**
Yeahsil Moon	212-326-3939
Reg. No. 52,042	**Telephone Number**
Printed or Typed name	

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

PTO/SB/80 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

☑ Practitioners associated with the Customer Number: 84802

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name			
Address			
City		State	Zip
Country			
Telephone		Email	

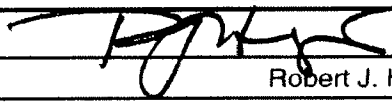
Assignee Name and Address:

Celgene Corporation
86 Morris Avenue
Summit, New Jersey 07901

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date	March 24, 2009
Name	Robert J. Hugin	Telephone	908-673-9000
Title	Chief Operating Officer and President		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	6612934
Application Number:	12229074
International Application Number:	
Confirmation Number:	7450
Title of Invention:	Methods for treating multiple myeloma using 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3dione
First Named Inventor/Applicant Name:	Jerome B. Zeldis
Customer Number:	20583
Filer:	Yeahsil Moon/Rochelle Flowers
Filer Authorized By:	Yeahsil Moon
Attorney Docket Number:	9516-773-999
Receipt Date:	10-DEC-2009
Filing Date:	19-AUG-2008
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Application Type:	Utility under 35 USC 111(a)

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Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	POA_w_373b_statement.pdf	131634 a2bdee61329e5f24917d839a3bf45d41ee505ed1	no	2

Warnings:	
Information:	

Total Files Size (in bytes):	131634

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/229,074	08/19/2008	Jerome B. Zeldis	9516-773-999

CONFIRMATION NO. 7450

84802
JONES DAY
222 E. 41ST. STREET
NEW YORK, NY 10017

POA ACCEPTANCE LETTER

OC000000039276256

Date Mailed: 12/23/2009

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/10/2009.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/hchristian/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/229,074	08/19/2008	Jerome B. Zeldis	9516-773-999	7450

84802 7590 06/24/2010

JONES DAY
222 E. 41ST. STREET
NEW YORK, NY 10017

EXAMINER	
SIMMONS, CHRIS E	
ART UNIT	**PAPER NUMBER**
1612	
MAIL DATE	**DELIVERY MODE**
06/24/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	12/229,074	ZELDIS, JEROME B.	
	Examiner	Art Unit	
	CHRIS E. SIMMONS	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-56* is/are pending in the application.

4a) Of the above claim(s) *31 and 54-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-30 and 32-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/19/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Claim 22 is generic to the following disclosed patentably distinct species: the multitude of structurally and chemically distinct compounds and materially distinct therapies encompassed by the claims. The species are independent or distinct because as disclosed the different species have mutually exclusive characteristics for each identified species. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

In order to be completely responsive to this specie election, applicant is required to elect whether a second agent is present and a specie of said agent if present. Applicant is further required to elect whether a therapy is present and which therapy if present.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Oral Election Was Made

During a telephone conversation with Yeah Sil-Moon on 06/10/2010 a provisional election was made without traverse to prosecute the invention of the presence of the second agent, dexamethasone, and the further administration of immunotherapy. Affirmation of this election must be made by applicant in replying to this Office action. Accordingly, claims 31 and 54-56 are withdrawn as being drawn to non elected subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 22-30 and 33-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over USP 5,635,517 in view of Davies et al., the combination taken further in view of USP 6,555,554.

The primary reference discloses, in the abstract, the treatment of multiple myeloma (MM) with thalidomide and dexamethasone. Thalidomide was administered in an initial dosage of 200 mg/d for 2 weeks and then increased as tolerated (in 200-mg increments at 2-week intervals) to a maximum daily dose of 800 mg. Dexamethasone was given orally in a dosage of 40 mg/d on days 1 through 4, 9 through 12, and 17 through 20 in odd cycles and 40 mg/d on days 1 through 4 in even cycles at monthly intervals. Patients with smoldering, indolent and relapsed myeloma showed results for thalidomide treatment. Signs of toxicity showed in some patients receiving 400 mg/day of thalidomide and the dosage had to be decreased, suggesting that the dosages must be altered depending on the side effects (see first paragraph on page 587). Table 2 at page 586 provides for potential strategies using thalidomide in MM treatment: Thalidomide may be used to treat MM in combination therapy with prednisone, vincristine, doxorubicin, melphalan, biological agents such as alpha2-interferon. The primary reference does not expressly teach ACTIMID.

The secondary reference discloses that Thalidomide (Thal) and Thal analogues (IMiDs) can act directly on MM cells. These drugs induce a dose-dependent inhibition of proliferation even in MM cell lines and patient MM cells resistant to conventional

chemotherapy, and they add to the effect of dexamethasone (Dex). For many years the immunomodulatory effects of Thal have provided the rationale for its use in the treatment of a broad range of diseases. Its mechanism of action was initially thought to be through the inhibition of cytokine production by monocytes, particularly tumor necrosis factor-alpha. New analogues of Thal have been produced that are 50,000 times more potent than Thal at inhibiting TNF-a secretion from peripheral blood mononuclear cells. (See page 210, columns 1 and 2). The authors concluded that their results show that Thal and its analogues may not only be useful in the treatment of refractory/relapsed disease, but also be effective in the maintenance of minimal residual disease after transplantation by enhancing NK-cell–mediated anti–MM cell immunity (page 216, column 2, last sentence). The secondary reference does not expressly teach ACTIMID.

The tertiary reference discloses a composition comprising a therapeutic agent and 1 to 100 mg of ACTIMID (Examples 14 and 15), or its enantiomers, in a single or multidose regimen to reduce TNF-alpha and to improve oncogenic or cancerous conditions. The reference does not expressly teach treating MM.

It would have been obvious to use the Thal analogue, ACTIMID, in the cyclical treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that the thalidomide analogue, ACTIMID, which is effective in decreasing TNF-alpha as disclosed in the tertiary reference would also be effective in the treatment of MM since the decrease in TNF-alpha provided the rationale for treating many disease with Thal as disclosed in the secondary reference,

including cancers, and more particularly, the cyclical treatment of MM as disclosed in the primary reference.

It would have been obvious to one of ordinary skill in the art to use the Thal derivative, ACTIMID, in the dosage regimen disclosed in the primary reference. The motivation would have also been the reasonable expectation of success in the treatment of MM using ACTIMID in a known effective dosage regimen. It is within the skill of the skilled artisan to adjust the regimen depending on the level of disease of the patient and the potency of the drug being used.

One of ordinary skill in the art would have found it obvious to adjust the amount of the drug depending on its efficacy and side effects as outlined in the primary reference (see first paragraph on page 587). Accordingly, the differences in claimed amount from the amounts disclosed in the reference will not support the patentability unless there is evidence indicating such amount is critical. *See MPEP 2144.05 [R-5] II A*.

Claims 22-30 and 33-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over USP 5,635,517 in view of Davies et al., the combination taken further in view of USP 6,281,230.

The disclosures of the primary and secondary references are outlined *supra.* The combination does not expressly teach ACTIMID.

The tertiary reference discloses combination therapy comprising administering between 1 to 100 mg of ACTIMID (Examples 14 and 15) and its enantiomers and an

active agent in the treatment of an oncogenic or cancerous condition (claims 18-26). It is further disclosed that ACTIMID is effective in decreasing TNF-alpha (paragraph bridging columns 4 and 5). The reference does not expressly teach treating MM.

It would have been obvious to use the Thal analogue, ACTIMID, in the cyclical treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that the thalidomide analogue, ACTIMID, which is effective in decreasing TNF-alpha as disclosed in the tertiary reference would also be effective in the treatment of MM since the decrease in TNF-alpha provided the rationale for treating many disease with Thal as disclosed in the secondary reference, including cancers, and more particularly, the cyclical treatment of MM as disclosed in the primary reference.

It would have been obvious to one of ordinary skill in the art to use the Thal derivative, ACTIMID, in the dosage regimen disclosed in the primary reference. The motivation would have also been the reasonable expectation of success in the treatment of MM using ACTIMID in a known effective dosage regimen. It is within the skill of the skilled artisan to adjust the regimen depending on the level of disease of the patient and the potency of the drug being used.

One of ordinary skill in the art would have found it obvious to adjust the amount of the drug depending on its efficacy and side effects as outlined in the primary reference (see first paragraph on page 587). Accordingly, the differences in claimed amount from the amounts disclosed in the reference will not support the patentability

unless there is evidence indicating such amount is critical. *See MPEP 2144.05 [R-5] II A*.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 22-30 and 33-53 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18-26 of Patent No. 6,281,230 in view of U.S. Patent No. 5,635,517 and Davies et al. The references' disclosures are outlined above. It would have been obvious to use ACTIMID in the treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that a thalidomide analogue effective in decreasing TNF-alpha would also be effective in the treatment of MM since the decrease in TNF-alpha has provided the rationale for treating many disease with Thal, including cancers, and more particularly, MM.

Claims 22-30 and 33-53 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,555,554 in view of U.S. Patent No. 5,635,517, Davies et al. The disclosures of the first 3 references are outlined above. It would have been obvious to use ACTIMID in the treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that a thalidomide analogue

effective in decreasing TNF-alpha would also be effective in the treatment of MM since the decrease in TNF-alpha has provided the rationale for treating many disease with Thal, including cancers, and more particularly, MM.

Claims 22-30 and 33-53 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 7,119,106 in 230 in view of U.S. Patent No. 5,635,517 and Davies et al.

The patented claims disclose a composition comprising 1 to 100 mg of ACTIMID. The patent teaches that the compounds of the invention are effective in decreasing TNF-alpha (paragraph bridging col. 4 and 5). The patent does not expressly teach treating MM. It would have been obvious to use ACTIMID in the treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that a thalidomide analogue effective in decreasing TNF-alpha would also be effective in the treatment of MM since the decrease in TNF-alpha has provided the rationale for treating many disease with Thal, including cancers, and more particularly, MM.

Claims 22-30 and 33-53 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 7,189,740 in view of U.S. Patent No. 5,635,517 and Davies et al.

The references' disclosures are outlined above. It would have been obvious to use ACTIMID in the treatment of MM at the time of the invention. One of ordinary skill

in the art would have been motivated by the reasonable expectation that a thalidomide analogue effective in decreasing TNF-alpha would also be effective in the treatment of MM since the decrease in TNF-alpha has provided the rationale for treating many disease with Thal, including cancers, and more particularly, MM.

Claims 22-30 and 33-53 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 7,393,862 in view of U.S. Patent No. 5,635,517 and Davies et al.

The references' disclosures are outlined above. It would have been obvious to use ACTIMID in the treatment of MM at the time of the invention. One of ordinary skill in the art would have been motivated by the reasonable expectation that a thalidomide analogue effective in decreasing TNF-alpha would also be effective in the treatment of MM since the decrease in TNF-alpha has provided the rationale for treating many disease with Thal, including cancers, and more particularly, MM.

Conclusion

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRIS E. SIMMONS whose telephone number is (571)272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Chris E Simmons/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612

LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	ATTY DOCKET NO. 9516-773-999	APPLICATION NO To be assigned
	APPLICANT Zeldis	
	FILING DATE August 19, 2008	GROUP To be assigned

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	A01	2004/0122052	6/24/04	Muller, George et al.			
	A02	2004/0091455	5/13/04	Zeldis, Jerome B.			
	A03	2004/0087546	5/6/04	Zeldis, Jerome B.			
	A04	2004/0077686	4/22/04	Dannenberg, Andrew J. et al.			
	A05	2004/0077685	4/22/04	Figg, William D. et al.			
	A06	2004/0029832	2/12/04	Zeldis, Jerome B.			
	A07	2003/0235909	12/25/03	Hariri, Robert J. et al.			
	A08	2003/0191098	10/9/03	D'Amato, Robert J.			
	A09	2003/0187024	10/2/03	D'Amato, Robert			
	A10	2003/0181428	9/25/03	Green, Shawn J. et al.			
	A11	2003/0144325	7/31/03	Muller, George W. et al.			
	A12	2003/0139451	7/24/03	Shah, Jamshed H. et al.			
	A13	2003/0096841	5/22/03	Robarge et al.			
	A14	2003/0069428	4/10/03	Muller, George et al.			
	A15	2003/0045552	3/6/03	Robarge et al.			
	A16	2003/0028028	2/6/03	Man, Hon-Wah et al.			
	A17	2003/0013739	1/16/03	Masferrer et al.			
	A18	2002/0183360	12/5/02	Muller, George W. et al.			
	A19	2002/0173658	11/21/02	Muller, George W. et al.			
	A20	2002/0161023	10/31/02	D'Amato, Robert			
	A21	2002/0128228	9/12/02	Hwu			
	A22	2002/0061923	5/23/02	D'Amato, Robert			
	A23	2002/0054899	5/9/02	Zeldis, Jerome B.			
	A24	2002/0052398	5/2/02	D'Amato, Robert J.			
	A25	2002/0045643	4/18/02	Muller et al.			
	A26	2002/0035090	3/21/02	Zeldis et al.			
	A27	2001/0056114	12/27/01	D'Amato, Robert			
	A28	2001/0018445	8/30/01	Huang et al.			
	A29	6,555,554	4/29/03	Muller et al.			
	A30	6,518,298	2/11/03	Green et al.			
	A31	6,476,052	11/5/02	Muller et al.			
	A32	6,469,045	10/22/02	D'Amato			
	A33	6,458,810	10/1/02	Muller et al.			
	A34	6,420,414	7/16/02	D'Amato			
	A35	6,403,613	6/11/02	Man et al.			
	A36	6,395,754	5/28/02	Muller et al.			

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.S./

	A37	6,380,239	4/30/02	Muller et al.			
	A38	6,335,349	1/1/02	Muller et al.			
	A39	6,326,388	12/4/01	Man et al.			
	A40	6,316,471	11/13/01	Muller et al.			
	A41	6,281,230	8/28/01	Muller et al.			
	A42	6,235,756	5/22/01	D'Amato			
	A43	6,140,346	10/31/00	Andrulis, Jr. et al.			
	A44	6,114,355	9/5/00	D'Amato			
	A45	6,071,948	6/6/00	D'Amato			
	A46	6,020,358	2/1/00	Muller et al.			
	A47	5,955,476	9/21/99	Muller et al.			
	A48	5,929,117	7/27/99	Muller et al.			
	A49	5,877,200	3/2/99	Muller			
	A50	5,874,448	2/23/99	Muller et al.			
	A51	5,798,368	8/25/98	Muller et al.			
	A52	5,733,566	3/31/98	Lewis			
	A53	5,731,325	3/24/98	Andrulis, Jr. et al.			
	A54	5,712,291	1/27/98	D'Amato			
	A55	5,698,579	12/16/97	Muller			
	A56	5,674,533	10/7/97	Santus et al.			
	A57	5,639,476	6/17/97	Oshlack et al.			
	A58	5,635,517	6/3/97	Muller et al.			
	A59	5,629,327	5/13/97	D'Amato			
	A60	5,593,990	1/14/97	D'Amato			
	A61	5,591,767	1/7/97	Mohr et al.			
	A62	5,580,755	12/3/96	Souza			
	A63	5,528,823	6/25/96	Rudy, Jr. et al.			
	A64	5,393,870	2/28/95	Deeley et al.			
	A65	5,391,485	2/21/95	Deeley et al.			
	A66	5,385,901	1/31/95	Kaplan et al.			
	A67	5,354,556	10/11/94	Sparks et al.			
	A68	5,229,496	7/20/93	Deeley et al.			
	A69	5,134,127	7/28/92	Stella et al.			
	A70	5,120,548	6/9/92	McClelland et al.			
	A71	5,073,543	12/17/91	Marshall et al.			
	A72	5,059,595	10/22/91	Le Grazie			
	A73	4,999,291	3/12/91	Souza			
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		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
	B01	PCT/US03/11578		PCT				
	B02	WO 02/064083	8/22/02	PCT				
	B03	WO 02/059106	8/1/02	PCT				
	B04	WO 01/70275	9/27/01	PCT				
	B05	WO 01/087307	11/22/01	PCT				
	B06	WO 98/54170	12/3/98	PCT				
	B07	WO 98/03502	1/29/98	PCT				
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EXAMINER /Chris Simmons/	**DATE CONSIDERED** 06/18/2010

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with **MPEP 609**; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.S./

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12229074	ZELDIS, JEROME B.
	Examiner	Art Unit
	CHRIS E SIMMONS	1612

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
GOOGLE, EAST, PUBMED, INVENTOR SEARCHES COMPLETE	06/14/2010	CSIMMONS

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

ELECTRONIC FILING

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Jerome B. Zeldis	Confirmation No.: 7450
Serial No.: 12/229,074	Group Art Unit: 1612
Filed: August 19, 2008	Examiner: Simmons, Chris E.
For: METHOD FOR TREATING MULTIPLE MYELOMA USING 4-(AMINO)-2-(2,6-DIOXO(3-PIPERIDYL))-ISOINDOLINE-1,3-DIONE (as amended)	Attorney Docket No.: 9516-773-999 (CAM: 501872-999773)

AMENDMENT AND RESPONSE

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to Office Action dated June 24, 2010, Applicant submits the following amendment and remarks for the consideration by the Examiner and entry into the record of the above-captioned application. Submitted herewith are Supplemental Information Disclosure Statement with fee, and Petition for extension of term from September 24, 2010 to and including December 27, 2010 with fee.

Amendments to the Claims are reflected in the listing of the claims that begins on page 2 of this paper.

Remarks begin on page 6 of this paper.

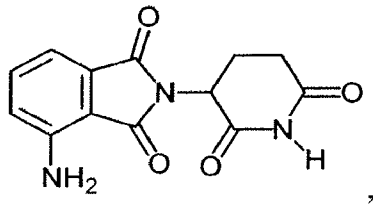
Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of the Claims:

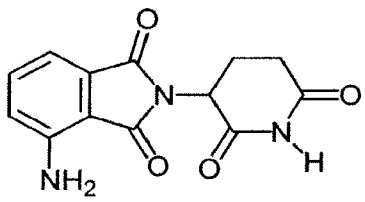
Claims 1-21. (canceled)

22. (currently amended) A method of treating multiple myeloma, which comprises administering to a patient having multiple myeloma from about [[0.1]] 0.5 mg to about [[10]] 4 mg per day of 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione of the formula:



or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

23. (previously presented) The method of claim 22, wherein the compound is



24. (previously presented) The method of claim 22, wherein the compound is a pharmaceutically acceptable salt.

25. (previously presented) The method of claim 22, wherein the compound is a pharmaceutically acceptable solvate.

26. (previously presented) The method of claim 22, wherein the compound is a pharmaceutically acceptable stereoisomer.

27. (previously presented) The method of claim 26, wherein the stereoisomer is an enantiomerically pure R isomer.

28. (previously presented) The method of claim 26, wherein the stereoisomer is an enantiomerically pure S isomer.

29. (previously presented) The method of claim 22, which further comprises administering a therapeutically effective amount of a second active agent.

30. (currently amended) The method of claim 29, wherein the second active agent is ~~hematopoietic growth factor, a cytokine, or~~ an anti-cancer agent.

31. (withdrawn) The method of claim 29, wherein the second active agent is granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), erythropoietin (EPO), interleukin (IL) or interferon (IFN), or a combination thereof.

32. (currently amended) The method of claim 29, wherein the second active agent is ~~oblimersen, melphalan, topotecan, pentoxifylline, taxotere, irinotecan, ciprofloxacin,~~ dexamethasone~~, doxorubicin, vincristine, dacarbazine, Ara-C, vinorelbine, prednisone, cyclophosphamide, bortezomib or arsenic trioxide, or a combination thereof~~.

33. (currently amended) The method of claim 22, which further comprises administering ~~radiation therapy, hormonal therapy, biological therapy or~~ immunotherapy.

34. (currently amended) The method of claim 22, wherein the multiple myeloma is relapsed, refractory or resistant to ~~conventional~~ previous therapy.

35. (previously presented) The method of claim 22, wherein the compound is administered orally.

36. (previously presented) The method of claim 35, wherein the compound is administered in the form of a capsule or tablet.

37. (currently amended) The method of claim 22, wherein the compound is administered in an amount of from about [[0.5]] 2 mg to about [[5]] 4 mg per day.

38. (currently amended) The method of claim 22, wherein the compound is administered in an amount of about 0.5 mg, 1.5 mg, 2 mg, or 4 mg~~, and 5 mg~~ per day.

39. (previously presented) The method of claim 22, wherein the compound is administered in an amount of from about 0.5 mg to about 2 mg per day.

40. (currently amended) The method of claim 22, wherein the compound is administered in an amount of about [[1]] 2 mg per day.

41. (previously presented) The method of claim 22, wherein the compound is administered cyclically.

42. (currently amended) The method of claim 41, wherein one cycle comprises four ~~to six~~ weeks.

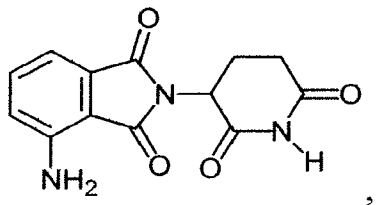
43. (previously presented) The method of claim 41, wherein one cycle comprises the administration of the compound for 21 days followed by seven days rest.

44. (currently amended) The method of claim 41, wherein the compound is administered ~~for four to twenty-four weeks with one to six weeks of rest~~ in an amount of about 2 mg daily on days 1 through 28 in a 28 day cycle.

45. (currently amended) The method of claim 22, wherein the compound is administered in an amount of from about 0.5 mg to about [[5]] 2 mg per day for 21 days followed by seven days rest in a 28 day cycle.

46. (previously presented) The method of claim 22, wherein the multiple myeloma is smoldering myeloma, indolent myeloma, chemotherapy responsive multiple myeloma, refractory myeloma, relapsed myeloma, or relapsed and refractory Dune-Salmon stage III multiple myeloma.

47. (currently amended) A method of treating multiple myeloma, which comprises administering orally to a patient having multiple myeloma from about [[0.1]] 0.5 mg to about [[10]] 4 mg per day of 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione of the formula:



or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, and a therapeutically effective amount of dexamethasone.

48. (currently amended) The method of claim 47, wherein the compound is orally administered in an amount of from about 0.5 mg to about [[5]] 4 mg per day for 21 days followed by seven days rest in a 28 day cycle; and dexamethasone is orally administered in an amount of about 40 mg once daily on days 1, 8, 15 and 22 ~~1 to 4, 9 to 12, and 17 to 20~~ of each cycle. ~~for first 4 cycles, and after the first 4 cycles dexamethasone is orally administered in an amount of about 40 mg once daily on days 1 to 4 of each cycle.~~

49. (currently amended) The method of claim 47, wherein the compound is orally administered in an amount of ~~from about 0.5 mg to about 5~~ 2 mg per day for 21 days followed by seven days rest in a 28 day cycle; and dexamethasone is orally administered in an amount of about 40 mg once daily on days 1, 8, 15 and 22 ~~1 to 4, 9 to 12, and 17 to 20~~ every 28 days.

50. (currently amended) The method of claim 47, wherein the compound is orally administered in an amount of from about 0.5 mg to about [[5]] 4 mg per day on days 1 through 28 in a 28 day cycle and dexamethasone is orally administered in an amount of about 40 mg once daily on days 1, 8, 15 and 22 ~~1 to 4~~ every 28 days.

51. (currently amended) The method of claim 47, wherein the compound is orally administered in an amount of ~~from about 0.5 mg to about 5~~ 2 mg per day on days 1 through 28 in a 28 day cycle and dexamethasone is orally administered in an amount of about 40 mg once daily on days 1, 8, 15 and 22 every 28 days.

52. (currently amended) The method of claim 47, wherein the compound is orally administered in an amount of from about 0.5 mg to about [[5]] 4 mg per day on days 1 through 28 in a 28 day cycle and dexamethasone is orally administered in an amount of about 40 mg once [[daily]] weekly.

53. (previously presented) The method of claim 36, wherein the capsule comprises the compound, lactose anhydrous, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

54. (withdrawn) The method of claim 22, which further comprises administering a therapeutically effective amount of doxorubicin and vincristine.

55. (withdrawn) The method of claim 22, which further comprises administering a therapeutically effective amount of melphalan.

56. (withdrawn) The method of claim 22, which further comprises administering a therapeutically effective amount of melphalan and prednisone.

REMARKS

I. Amendments to the Claims

Claims 1-21 were previously canceled without prejudice. Claims 22, 30, 32, 33, 34, 37, 38, 40, 42, 44, 45, and 47-52 have been amended to clearly define the subject matter of the invention. No new matter has been added. Applicant reserves the right to prosecute the subject matter of any canceled claims in one or more continuation, continuation-in-part, or divisional applications.

II. Response to the Restriction Requirement and Election

The Office Action required to elect a species of a second active agent and a further therapy, if present (pages 2-4 of the Action). Applicant provisionally elects dexamethasone as a second active agent and immunotherapy as a further therapy, for examination. Following entry of the present Amendment, the pending claims encompassing the elected invention are claims 22–30 and 32-53.

Applicant reserves the right to rejoin claims to non-elected species, for example, upon the allowance of a generic claim. Applicant also reserves the right to prosecute any non-elected subject matter in one or more continuation, continuation-in-part, or divisional applications.

III. The Claimed Invention is Not *Prima Facie* Obvious

The rejection over the combination of '517 Patent, Davies and '554 Patent

Claims 22-30 and 33-53 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,635,517 ("'517 Patent") in view of Davies *et al.* (*Blood*, 2001, "Davies"), the combination taken in view of U.S. Patent No. 6,555,554 ("'554 Patent"). (Pages 5-7 of the Action). Applicant respectfully traverses the rejection.

The Office alleges that the primary reference discloses the treatment of multiple myeloma with thalidomide and dexamethasone, in the abstract, pages 586 and 587. (Page 5 of the Action). The Office also alleges that the secondary reference teaches that thalidomide and its IMiDs® analogues can act directly on multiple myeloma cells, and that new analogues are 50,000 times more potent than thalidomide in inhibiting TNF-α. (Pages 5-6 of the Action). The Office further alleges that the tertiary reference discloses a composition comprising a therapeutic agent and 1 to 100 mg of ACTIMID to reduce TNF-α and to improve oncogenic or cancerous conditions. (The Action, page 6).

Specifically, the Office alleges that "one of ordinary skilled in the art would have been motivated by the reasonable expectation that the thalidomide analogue, ACTIMID,

which is effective in decreasing TNF-α as disclosed in the tertiary reference, would also be effective in the treatment of multiple myeloma, since the decrease in TNF-α provided the rationale for treating many diseases with Thal as disclosed in the secondary reference including cancers, and more particularly, the cyclical treatment of multiple myeloma as disclosed in the primary reference." Pages 6-7 of the Action. Applicant disagrees.

Applicant assumes that the PTO refers '517 Patent as the primary reference, Davies as the secondary reference, and '554 Patent as the tertiary reference for this rejection, in view of the page numbers of the second reference and column numbers of the tertiary reference that are mentioned in the Action.

However, there are no abstract, pages 586 and 587 in the '517 Patent (the primary reference) that disclose the treatment of multiple myeloma with thalidomide and dexamethasone, much less the cyclical treatment, as the PTO alleges is disclosed in the primary reference. (*See* page 5 of the Action). Thus, the primary reference is misplaced. For this reason alone, the rejection fails. Applicant respectfully requests that the rejection be withdrawn. [1]

The claimed invention relates, *inter alia*, to specific methods of treating multiple myeloma by administering specific amounts (about 0.5 to 4 mg/day) of a specific compound known as 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (pomalidomide or Actimid®). The claimed invention also relates to very specific combination therapy with dexamethasone and cyclic dosing regimen.

The primary reference fails to suggest the treatment of multiple myeloma within these claimed methods. The PTO admits that the primary reference does not teach ACTIMID (page 5 of the Action). Thus, the primary reference does not direct the skilled person to use the recited compound in the treatment of multiple myeloma.

Next, the Office's reliance on the secondary reference (Davies) does not cure the defects of the primary reference. The Office alleges that "one of ordinary skilled in the art would have been motivated by the reasonable expectation that the thalidomide analogue, ACTIMID, would also be effective in the treatment of multiple myeloma, since the decrease in TNF-α provided the rationale for treating many diseases with Thal as disclosed in the secondary reference including cancers" (pages 6-7 of the Action).

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[1] Applicant called the Examiner to clarify the reference. The Examiner admitted the misplacement of the reference and stated that he would withdraw the Office Action. However, Applicant has not received Notice of Withdrawal of the Office Action yet.

However, TNF-α inhibition is not what Davies discusses as an important factor in studying the compounds in multiple myeloma. Instead, Davies studied other mechanisms such as immunomodulatory effects (*e.g.*, natural killer cell cytotoxicity) of thalidomide and its derivatives in multiple myeloma (pages 213-216). Davies explicitly states that the rational for the use of thalidomide in multiple myeloma was anti-angiogenesis, not TNF-α. *See* page 210, abstract ("The angiogenic activity of thalidomide, coupled with an increase in bone marrow angiogenesis in multiple myeloma, provided the rational for the use of thalidomide in multiple myeloma"). A person of ordinary skill in the art would have had *no* motivation to choose more potent TNF-α inhibitors in treating multiple myeloma, because decreasing TNF-α was not considered as motivating factor in multiple myeloma studies in Davies.

Further, Applicant submitted several publications showing that potent known TNF-α inhibitors failed in treating multiple myeloma. For example, Enbrel® is a well known TNF-α antagonist. *See* Tsimberdou (IDS Reference C223), page 375. Ten patients with refractory multiple myeloma were treated with Enbrel®. Enbrel® did not have anti-myeloma activity. *Id.* Also, see Kast (IDS Reference C222). Thus, not all TNF-α inhibitors treat multiple myeloma.

Therefore, Davies does not provide a rationale for treating multiple myeloma based on TNF-α activity. The PTO's reliance on Davies is misplaced, and the rationale for this rejection is factually incorrect.

Moreover, irrespective of mechanisms, there is no suggestion in Davies that the instant compound is effective to treat multiple myeloma, much less suggestion to combine it with dexamethasone and cyclic treatment. Davies merely discloses that the compounds studied are thalidomide, and 3 other IMiDs® or immunomodulatory compounds (IMiD1, IMiD2 and IMiD3).[2] *See*, page 212. Without identifying thalidomide analogs by their chemical structures or chemical names, Davies used the general terms, IMiD1, IMiD2, and IMiD3 to identify the compounds. In fact, the Office admits that the secondary reference does not teach ACTIMID. (Page 6 of the Action).

In addition, Davies does not suggest that the instant compound is more effective than thalidomide in the treatment of multiple myeloma. There would be no basis in Davies

[2] Applicant respectfully submits that IMiDs® refers to Celgene Corporation's registered trademark for its proprietary immunomodulatory compounds.

to select one compound over the other. Thus, Davies would not lead one skilled in the art to select the instant compound. For this additional reason, the rejection fails.

As to the tertiary reference, the Office admits that that the tertiary reference does not teach treating multiple myeloma. (Page 6 of the Action). The claimed methods require treating multiple myeloma with the specific amounts (0.5 to 4 mg/day) of the recited compound by specific dosing regimens. All the claim elements must be considered in a 103 rejection. Applicant points out that the PTO has not borne the burden of establishing *prima facie* obviousness against the claims as a whole.

Therefore, the PTO has provided no specific source of motivation to combine the teachings of the three references in the particular claimed manner. *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1379 (Fed. Cir. 2006). Further, even if the cited references were combined as the PTO alleges, the combination would not have provided the requisite expectation of success. Such is required to establish a *prima facie* case of obviousness. *See e.g., PharmaStem* at 1360 (Fed. Cir. 2007). When the cited references are combined, one skilled in the art is merely taught that thalidomide may be used for treating multiple myeloma or that certain unidentified immunomodulatory compounds can be explored further. However, the combination of the references would not have provided any indication to use specific amounts (0.5 to 4 mg/day) of the recited compound for treating multiple myeloma, much less the combination therapy with dexamethasone by specific dosing regimens. Because the Office has not demonstrated such, the claimed invention is not obvious by the combination of the cited references.

Nonetheless, the PTO contends that it would be obvious to adjust the amount of the drug depending on its efficacy and side effects as disclosed in the primary reference for thalidomide (page 587). (Page 7 of the Action). Applicant respectfully disagrees.

As discussed above, there is no page 587 in the primary reference, much less such disclosure or suggestion for the amounts of thalidomide. Thus, the reason for the rejection cannot sustain. Contrary to the PTO, MacNeil (2010) establishes that the claimed dose is not suggested or obvious by on the cited art. Applicant submits herewith a copy of MacNeil as Exhibit 1. MacNeil describes that "small differences in structure of pomalidomide from thalidomide mean very important differences in terms of side effect profiles, efficacy, and potency."

Therefore, a skilled artisan would have no reason to use the claimed dose (0.5-4.0 mg/d) of the instant compound (pomalidomide) from the cited art. The Office Action has not pointed to any reason that would have prompted a person skilled in the art to

specifically select specific amounts of the claimed compound for treating multiple myeloma as claimed. The PTO has also not demonstrated a reasonable expectation of success in doing so. *See e.g., PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d at 1342, 1360 (Fed. Cir. 2007); *see also Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1090 (Fed. Cir. 2008).

In view of the foregoing, a *prima facie* case of obviousness has not been established, and the rejection under 35 U.S.C. § 103(a) must be withdrawn.

The rejection over the combination of '517 Patent, Davies and '230 Patent

Claims 22-30 and 33-53 are rejected as being unpatentable over the '517 Patent, in view of Davies, the combination taken further in view of U.S. Patent No. 6,281,230 ("'230 Patent"). (Pages 7-8 of the Action). Applicant respectfully traverses the rejection.

The Office repeated the same allegation that "one of ordinary skilled in the art would have been motivated by the reasonable expectation that the thalidomide analogue, ACTIMID, which is effective in decreasing TNF-α as disclosed in the tertiary reference would also be effective in the treatment of multiple myeloma, since the decrease in TNF-α provided the rationale for treating many diseases with Thal as disclosed in the secondary reference including cancers, and more particularly, the cyclical treatment of multiple myeloma as disclosed in the primary reference." Page 8 of the Action. Applicant disagrees.

Applicant assumes that the Examiner refers to the '517 Patent as the primary reference, Davies as the secondary reference, and the '230 Patent as the tertiary reference. The '517 Patent and Davies have been discussed above. There are no disclosure or suggestion for the treatment of multiple myeloma with thalidomide and dexamethasone, much less the cyclical treatment, as the PTO alleges is disclosed in the primary reference. It appears that without proper analyses of the cited references, the PTO simply repeated the same allegations in this rejection. For this reason alone, the rejection fails and it must be withdrawn.

The '230 Patent does not cure the lack of teaching or suggestion of the claimed methods. The Office alleges that the tertiary reference discloses combination therapy comprising administering 1 to 100 mg of ACTIMID in treating oncogenic or cancerous condition and in decreasing TNF-α. (Pages 7-8 of the Action). The '230 Patent is the same family as the '517 Patent, and adds nothing to change the errors in the rejections already pointed out.

Therefore, for the same reasons as discussed above, a *prima facie* case of obviousness has not been established. Applicant respectfully requests that the rejection be withdrawn.

Unexpected Results Support the Nonobviousness of the Instant Claims

Further, even assuming, *arguendo*, a *prima facie* case of obviousness is established by the cited references in combination, Applicant submits evidence of unexpected results of the claimed method sufficient to rebut a *prima facie* case of obviousness. *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, 348 F.Supp.2d 713, 755 (N.D.W.Va. 2004); and *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

The Examiner is required to consider all rebuttal evidence including unexpected results submitted by Applicant. *See In re Sullivan*, 498 F.3d 1345, 1351 (Fed. Cir. 2007), citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir. 2007); MPEP §2145. This requirement remains unchanged following the decision in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007), as the Federal Circuit has made clear in *In re Sullivan*. 498 F.3d at 1351.

Applicant respectfully invites the Examiner's attention to MacNeil, 2010 (Exhibit 1); Lacy *et al.*, *Leukemia*, 2010 (Exhibit 2); Lacy *et al.*, *J. Clin. Oncol.*, 2010 (Exhibit 3); Lacy *et al.*, *J. Clin. Oncol.*, 2009 (Exhibit 4); and Lacy *et al.*, *ASH Abstract #863*, 2010 (Exhibit 5), copies of which are submitted herewith. MacNeil reports on monotherapy of the instant compound (pomalidomide), and combination therapy with dexamethasone in multiple myeloma patients, with response rates of 50% or better in heavily pretreated patients. MacNeil describes that small differences in structure of pomalidomide from thalidomide mean very important differences in terms of side effect profiles, efficacy, and potency.

Further, Lacy *et al.* disclose clinical studies where multiple myeloma patients were administered the instant compound in combination with dexamethasone. *See* Lacy *et al.* Exhibits 2-5. The authors discussed that the studies showed the impressive activity of pomalidomide in patients who were refractory to other agents including thalidomide. Lacy *et al.*, 2009, Exhibit 4, at pages 4-5. The authors concluded that the therapy was extremely active, and well tolerated in the treatment of relapsed/refractory multiple myeloma, including high response rates in patients refractory to other agents. Exhibit 4 at pages 1 and 5, and Exhibit 5.

These publications clearly demonstrate unexpected results of the claimed therapy for multiple myeloma. As the Court explained, "[w]hen a patent applicant puts forth rebuttal evidence, the Board must consider that evidence." *In re Sullivan*. 498 F.3d at 1351. Applicant respectfully submits that these results are sufficient to rebut any presumption of obviousness that may have been established by the references cited in the Office Action. Thus, Applicant respectfully requests that the rejection under 35 U.S.C. §103 be withdrawn.

IV. The Double Patenting Rejections Should Be Withdrawn

Claims 22-30 and 33-53 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over (1) claims 18-26 of the '230 Patent in view of the '517 Patent and Davies; (2) claims 1-17 of the '554 Patent in view of the '517 Patent and Davies; (3) claims 1-7 of U.S. Patent No. 7,119,106 (the '106 Patent) in view of the '517 Patent and Davies; (4) claims 1-34 of U.S. Patent No. 7,189,740 (the '740 Patent) in view of the '517 Patent and Davies; and (5) claims 1-25 of U.S. Patent No. 7,393,862 (the '862 Patent) in view of the '517 Patent and Davies. (Pages 9-12 of the Action). Applicant respectfully traverses the rejections.

For the obviousness-type double patenting rejections, the Office stated the same reasons as for the rejections under 35 U.S.C. §103(a), by repeating the same phrases of pages 5-8 of the Action. See pages 9-12 of the Action. Applicant reiterates that the instant claims are not obvious over the cited Patents in view of the '517 Patent and Davies, for the reasons set forth above in responding to the rejections under 35 U.S.C. §103(a). The Examiner has not established a *prima facie* case for the same reasons as discussed above. Further, the obviousness-type double patenting rejections should be withdrawn in view of the submitted evidence for the unexpected results of the claimed invention.

Furthermore, the claims of the '230 Patent recite methods of treating inflammation, inflammatory disease, autoimmune disease, an oncogenic or cancerous condition, using amino-substituted 1-oxo-2-(2,6-dioxopiperidin-3-yl) isoindolines. The '230 Patent does not disclose or suggest the claimed methods for treating the specific disease multiple myeloma using the specific dose about 0.5-4 mg of pomalidomide per day, the combination therapy with dexamethasone, much less the specific cyclic dosing regimen, as recited in the pending claims. The Examiner has made no *prima facie* case that the pending claims are obvious over the claims of the '230 Patent. Further, unexpected results of the claimed method have been established and the rejection should be withdrawn.

The claims of the '554 Patent recite pharmaceutical compositions comprising lenalidomide, in combination with a pharmaceutically suitable carrier, in an amount sufficient to reduce the level of TNFα, improve an oncogenic or cancerous condition, reduce inflammation, or improve autoimmune disease; and methods of reducing undesirable levels of TNFα using amino-substituted 1-oxo-2-(2,6-dioxopiperidin-3-yl) isoindolines.

The '554 Patent does not disclose or suggest the claimed methods for treating multiple myeloma using about 0.5-4 mg of pomalidomide per day, the combination therapy with dexamethasone, much less cyclic dosing regimen, as recited in the pending claims. The Examiner has made no *prima facie* case that the pending claims are obvious over the claims of the '554 Patent. Further, unexpected results of the claimed invention have been established and the rejection must be withdrawn.

The claims of the '106 Patent recite pharmaceutical compositions comprising an effective amount of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione or acid addition salt thereof, and a pharmaceutically acceptable carrier, diluent or expient. The '106 Patent does not disclose or suggest the claimed methods for treating multiple myeloma using specific amounts of pomalidomide, as recited in the pending claims. The Examiner has made no *prima facie* case that the pending claims are obvious over the claims of the '106 Patent. Further, unexpected results of the claimed method have been established and the rejection should be withdrawn.

As to the '740 patent, Applicant submitted a terminal disclaimer in the '740 patent over the parent application of the instant application, on June 23, 2006, in responding to obviousness-type double patenting rejection issued during the prosecution of the '740 patent over the parent application of the instant application. In view of the terminal disclaimer, the rejection over the '740 patent is moot and should be withdrawn.

As to the '862 patent, Applicant submitted a terminal disclaimer in the '862 patent over the parent application of the instant application, on Sep. 5, 2006, in responding to obviousness-type double patenting rejection issued during the prosecution of the '862 patent over the parent application of the instant application. In view of the terminal disclaimer, the rejection over the '862 patent is moot and should be withdrawn.

Accordingly, all these rejections over the cited Patents under judicially created obviousness-type double patenting are moot. Applicant respectfully requests that the rejections be withdrawn.

V. Conclusion

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above amendment and remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Respectfully submitted,

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Evidence of a mechanism by which etanercept increased TNF-alpha in multiple myeloma: New insights into the biology of TNF-alpha giving new treatment opportunities-the role of bupropion

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Abstract

Etanercept is a commercially available pharmaceutical protein approved for treatment of rheumatoid arthritis, RA. Given subcutaneously, etanercept binds and inactivates soluble tumor necrosis factor-alpha, TNF. Etanercept has a good safety record and is of benefit in lowering pain, inflammation, and joint destruction in RA. RA is mediated by many factors, TNF among them. Malignant myeloma, MM, is a malignant clonal expansion of a post-germinal center B lymphocyte. Since TNF is a necessary growth factor for expansion and maintenance of MM cells, and etanercept binds soluble TNF and is of clinical benefit in RA, etanercept was tried experimentally in MM. Contrary to expectations, etanercept resulted in increased levels of TNF and possibly shortened survival. This paper presents an hypothesis of how this happened. There are two cognate receptors for TNF, termed R1 and R2 and two forms of TNF, soluble and transmembrane. Soluble TNF has greater affinity for TNF-R1 than for TNF-R2. Transmembrane TNF has equal affinity for the two receptors. Since TNF-R2 signaling tends to be more anti-apoptotic and activating of nuclear factor kappa B, NFkB, than is TNF-R1, and TNF-R1 tends to be more pro-apoptotic than is TNF-R2, by inactivating soluble TNF while leaving transmembrane TNF signaling relatively unchanged, etanercept changed the balance in TNF signaling from TNF-R1 towards TNF-R2 weighting. Anti-apoptosis and TNF synthesis would have been up-regulated by that shift. Early data indicates that the common generic antidepressant bupropion may ameliorate Crohn's disease course by down regulating TNF synthesis, maybe it will slow the course of MM as well.

Keywords: Apoptosis; Bupropion; Chronic lymphocytic leukemia; Crohn's disease; Etanercept; Inflammation; Multiple myeloma; Remission; Rheumatoid arthritis; Tumor necrosis factor-alpha

1. Introduction

"Common pathogenic mechanisms are shared between many human chronic inflammatory diseases of unrelated pathology and manifestations" [1] and tumor necrosis factor-alpha, TNF, "sits at the crossroads" of many of these common pathogenic mechanisms [1].

Etanercept is used to decrease TNF function [2]. It is in wide use as an effective and relatively safe treatment for rheumatoid arthritis, RA. Inflammation and joint destruction of RA are partly driven by TNF [1–3].

Etanercept induces remission or reduction of disease activity in RA by binding to and lowering soluble TNF activity [2,3]. Secondary symptoms of RA such as fatigue and malaise are also often diminished. There are two cognate receptors for TNF, termed TNF-R1 and TNF-R2. These will be discussed in greater detail later. Etanercept is a 150 kDa fusion protein, a dimeric (single) human IgG Fc portion fused with two ectodomains of TNF-R2. It is given by subcutaneous injection twice weekly, and has a half-life of 102 h.

Multiple myeloma, MM, is a malignant hematopoietic neoplasm where TNF also plays an important pathogenic role [4,5], and thalidomide is in increasingly common use in treating MM and is thought to work in part by lowering the excess TNF and other floridly elevated angiogenic and

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growth promoting cytokines in MM [5]. Tsimberidou et al. [6] therefore tried etanercept in the treatment of MM. Surprisingly, it increased circulating TNF amounts and may have shortened survival [6].

In this manuscript I will review the available literature and propose a hypothesis of how their reverse-from-expected result might have occurred. Although a negative trial, Tsimberidou et al. have provided indications of "proof-of-principle", if higher TNF hastened disease process, lowering TNF levels may well slow MM progression. Their work has given pivotal new insights into the biology of MM and points the way for immediately exploitable new treatments for MM as outlined below.

By discussing selected aspects of what is known about the signaling molecule TNF in its two forms, soluble, sTNF, and outer cell membrane bound (transmembrane) tmTNF, and TNF's two outer cell membrane receptors TNF-R1 and TNF-R2 it will be seen that the answer to the puzzle of Tsimberidou et al.'s unexpected findings lies in the interaction between these four elements of TNF signaling and etanercept's selective shifting of the balance between them.

2. Multiple myeloma

MM is a clonal malignancy of a post germinal center B lymphocyte [7,8]. Disease course is often in three stages: (1) A plasma cell clone acquires abnormally low apoptosis rate and accumulates, clinically recognized either as MM or monoclonal gammopathy of unknown significance. (2) Clonal expansion occurs in close proximity to bone marrow stroma cells that provide multiple growth (increased mitosis) and survival (decreased apoptosis) signals, among which prominently are TNF and interleukin-6, il-6. (3) In the terminal phase the malignant clone acquires marrow independence and consequent metastasis to extra-medullary sites.

Different morphological varieties of MM are recognized, most synthesize large amounts of IgG. In early and middle stages of MM, accretion is more by abnormally low apoptosis rate than by high mitotic rate [7,9], in this respect similar to non-Hodgkin's lymphoma, NHL [9], and B cell chronic lymphocyte leukemia, CLL [9], reviewed in [10]. Lower apoptosis rate is mediated in part by TNF [8,9,11]. TNF does so by several paths, one of which is activation of nuclear factor kappa B, NFkB (vide post) [12–14].

MM cells synthesize high levels of TNF [4,5,8,11] among a flood of other growth sustaining and osteoclastogenic cytokines. Circulating levels of TNF reflect and are roughly proportionate to total MM tumor mass [8] and enhanced expression of TNF correlates with enhanced aggressiveness [8].

3. Two forms of TNF

TNF (reviewed in [15–17] is a phylogenetically conserved signaling molecule synthesized by most cells of the body. Lymphocytes, myocytes, adiposites, epithelia, renal mesangial cells, and many other cell types are important producers. Monocyte lineage cells in their various forms are particularly prominent synthizers of TNF, examples: macrophages, astroglia, microglia, Kuppffer cells, Langerhans cells. TNF synthesis is both constitutive and stimulated.

TNF is pleiotropic. As a soluble circulating molecule, sTNF is 17 kDa and spontaneously forms non-covalently bound homotrimers. Only trimeric TNF can stimulate either of the two known cognate TNF receptors. TNF is first expressed as a transmembrane 26 kDa protein, tmTNF, by the cells synthesizing it. tmTNF must also trimerize before becoming active in stimulation of either TNF receptor. All sTNF is derived from tmTNF by proteolytic cleavage, the process termed ectodomain shedding. Not all tmTNF goes on to be cleaved to generate sTNF.

A good example of pleiotropism of relevance to MM is the data on sTNF versus tmTNF overfunction in the case of the heart [18–20]. Cardiomyocytes synthesize TNF. TNF is essential for normal myocardial modeling during embryogenesis and maintenance throughout the lifespan. Yet in rat models, TNF contributes to development of myocardium wall thinning and chamber dilation of dilated cardiomyopathy when over-expressed in soluble form, and contributes to wall thickening of hypertrophic cardiomyopathy when over-expressed in transmembrane form [18,19]. In this TNF and cardiomyopathy story, mechanistic similarities to the relationship of TNF signaling to MM will be seen and referred to later.

There are several levels on which to answer the question "What does TNF do?". Most literally the answer is, stimulate either TNF-R1 or TNF-R2 or, most commonly some variable proportion of both. Elimination of damaged or effete cells, embryological development and ontological processes generally require both the apoptosis induction function and the anti-apoptosis functions of TNF.

As clinicians we tend to think immunologically of how to get better attacks, to eliminate intruders, cancer, malaria, tuberculosis, etc and TNF is important in this role, in initiation of a vigorous immune response, both cellular and antibody, and in expansion of the required lymphocyte populations [16,21]. But an immune response that doesn't stop when the enemy is defeated becomes a problem too. Part of keeping the immune response quantitatively commensurate with antigen challenge is the phenomenon of activated T cell apoptosis. TNF appears again in this role among many other apoptosis furthering signal molecules, shutting off the immune response by inducing apoptosis in activated lymphocytes when the particular immune response is no longer needed [16,17,22].

4. Two TNF receptors

Two cognate receptors for TNF are recognized, TNF-R1 or p55, and TNF-R2 or p75 (reviewed in refs) [15–17,23,24].

TNF-R1:TNF-R2 protein ratio expressed on a cell's surface is one way a cell can direct the consequences of TNF signaling and effect fundamental outcome.

Although it is incorrect to strictly equate TNF-R1 stimulation with apoptosis induction and TNF-R2 stimulation with NFkB activation and consequent pro-inflammatory gene transcription, and anti-apoptosis effects, such a scheme is an approximation of what often happens. There are important exceptions and reverse cases [24].

So intracellular events after either TNF-R1 or TNF-R2 stimulation by (ligation of) either sTNF or tmTNF are complex, with engagement of signaling cascades with multiple branch points and amplification and squelching mechanisms. Strong, weak, or no cross-talk between the respective R1/R2 cascades can be seen in various cases but in all cases NFkB activation is an essential but not necessarily sufficient step in diverting the consequence of TNF from apoptosis to anti-apoptosis [12–14,16].

5. NFkB

NFkB refers to a group of five related dimeric proteins, resident, inactive, and anchored in the cytoplasm non-covalently complexed with iota kappa B, IKB [13,14]. IKB is a small protein that has the effect of retaining NFkB in cytoplasm. Upon TNF binding to either TNF-R1 or TNF-R2 a chain of cytoplasm proteins can be recruited and activated resulting in IKB phosphorylation. Phosphorylated IKB looses its affinity for NFkB which, thereby freed from its cytoplasmic anchor, migrates (is actively transported to ?) the nucleus.

TNF is one of dozens of proteins whose gene's transcription is stimulated by NFkB binding [13,15]. Since TNF-R1 stimulation tends to lead to an apoptosis weighted response and TNF-R2 stimulation to NFkB activation and NFkB regulated gene transcription, and TNF is one such gene product, TNF can stimulate its own synthesis predominently via R2. Increased tmTNF is seen after TNF-R2 weighted TNF signaling [24]. Multiple other positive and negative feedback TNF control paths have been identified ([25] for example). Although either TNF-R1 or TNF-R2 can result in NFkB activation, on molar ratio, TNF receptors activated per NFkB's activated for TNF-R2 tends to be high and TNF-R1's activated per NFkB's activated low [15,16]. Note that MM cells have documented supernormal levels of activated NFkB with consequent tonic over engagement of anti-apoptotic intracellular signaling [12].

6. The core observations

TNF-R2 has lower affinity for sTNF than does TNF-R1 [15–17,23,24]. sTNF therefore stimulates TNF-R1 more efficiently, more effectively, at lower molar ligand-to-receptor ratio, than it does TNF-R2. By some estimates as much as twenty fold differential. tmTNF stimulates TNF-R1 and TNF-R2 equally well.

Etanercept binds mainly to sTNF, little is found bound to tmTNF [26,27]. This may in certain clinical situations shift signaling relative weighting from TNF-R1 towards TNF-R2, given sTNF's greater affinity for R1 than for R2 and tmTNF's equal affinity for the two receptors [16,17,23,24]. With this weighting shift from TNF-R1 toward TNF-R2 after etanercept in MM, the anti-apoptosis forces that are more tightly coupled to TNF-R2 than to TNF-R1 are relatively furthered. Also activated to a greater degree will be NFkB regulated genes like that coding for TNF itself, the synthesis of which is then up-regulated. Note two self perpetuating, positive feedback aspects here, of TNF both engaging anti-apoptosis signaling paths (increasing cell number) and generation of more TNF itself (increased TNF synthesis).

Note the physiological similarity of the above explanation of etanercept in MM is consonant with rat cardiomyopathy data discussed earlier. Concentric cardiac hypertrophy, a disease of accretion, occurs with TNF-R2 over expression and cardiac wall thinning in dilated cardiomyopathy, a disease of cell loss, with targeted TNF-R1 over expression.

7. Other examples of TNF increase during etanercept

In 1995, one of the first published research reports on etanercept, long before its introduction into clinical practice, showed etanercept dose dependently increased circulating TNF in healthy humans given intravenous lipopolysaccharide (although total biologically active TNF was decreased in their bioassay system) [28]. In 2002, etanercept mediated increased T cell TNF secretion was observed in ankylosing spondylitis patients [29] even when they experienced excellent pain relief and clinical resolution of their illness [29]. In 2003 intracellular TNF was noted to be increased in both CD4+ and CD8+ T cells after in vitro stimulation of peripheral blood lymphocytes taken from patients with ankylosing spondylitis treated with etanercept compared to that of those not taking etanercept [30], the authors concluding that etanercept treatment results in up-regulation of lymphocytes' TNF synthesis [30]. In 2004 a trial of etanercept in patients with progressive metastatic breast cancer showed an increase of molecular TNF as soon as 24 h after injection [31]. Elevation persisted for the duration of etanercept treatment [31]. Note however molecular (immunoactive) TNF does not necessarily mean presence of physiologically (immunologically) active TNF.

8. TNF and Crohn's disease

Crohn's disease, CD, is a common disease of inflammatory mucosal erosions occurring anywhere along the alimentary tract. TNF driven apoptosis failure of gut intramural lymphocytes is a well documented central feature of CD [22,26,32].

An essential link in the development of overt CD is created when TNF becomes a survival signal for lamina propria lymphocytes to pathological degree, this paper suggests by a manner and mechanism similar to that outlined for MM. TNF-R1 to TNF-R2 switch of predominance on gut lamina propria lymphocytes' surface is seen in CD [17,32], just as it is on MM cells [11], corresponding to a switch from TNF induced apoptosis (TNF-R1 prominent) to a TNF-R2 (pro-survival, anti-apoptotic, NFkB activating) response.

Aphthous ulcers restricted to the mouth that are not associated with CD (canker sores), have similar pathophysiology to the initial superficial mucosal erosions in CD. Successful treatment of CD with phenelzine [33] was based in part on early clinical observations of Saul Rosenthal, reported in 1984 in the New England Journal of Medicine, that severe and recurrent oral aphthous ulcers not associated with CD resolved during phenelzine treatment [34].

Phenelzine is an antidepressant MAOI, monoamine oxidase inhibitor, in continuous use (as of summer 2005) since the mid 1950's. MAOI's retard catabolism of dopamine, epinephrine, norepinephrine, and serotonin, resulting in increased neuronal synaptic concentrations of these neurotransmitters, as is achieved by, but with different mechanism and with differing neurotransmitter profiles, the tricyclic antidepressants (like amitriptyline) or serotonin re-uptake inhibitors (like fluoxetine). Since MAOI's have potentially fatal interactions with other commonly used drugs and serious interactions with common foods, alternatives for treatment of CD were sought.

Bupropion is a small molecular weight (276 Da) non-MAOI antidepressant, that is off-patent, generically available, cheap, and in common use worldwide to treat depression. It has a synaptic neurotransmitter enhancing profile that among current antidepressants is most similar to phenelzine but has none of phenelzine's dangers. So bupropion was tried and indeed was found to be of strong benefit in CD [35,36]. Initial indications are bupropion lowers circulating TNF levels [37,38]. Furthermore, a recent case series report indicates bupropion, like phenelzine before it causes remission of non-CD related chronic recurrent aphthous ulcerations as well [39].

If bupropion lowering of TNF is confirmed it should be cautiously studied in MM.

9. Conclusions

Five studies show evidence of increased TNF synthesis during etanercept treatment [6,28–31]. This paper outlines a physiological path by which this might occur by shifting total TNF mediated signaling away from TNF-R1 towards TNF-R2 weighting, resulting in increased TNF synthesis, decreased apoptosis.

Preliminary data indicate that the generic antidepressant bupropion lowers TNF synthesis, resulting in balanced down-regulation of TNF-R1 and TNF-R2 signaling. If confirmed, trial of TNF lowering by bupropion is warranted in MM, where TNF signaling has been shown to serve as a growth factor and hasten disease progression.

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I have done this work myself and it was unfunded research. I have no commercial relationship with any entity related to any matter within or related to this paper. I have, however, applied for a patent on bupropion as a TNF lowering agent.

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Pilot study of recombinant human soluble tumor necrosis factor (TNF) receptor (p75) fusion protein (TNFR:Fc; Enbrel) in patients with refractory multiple myeloma: increase in plasma TNFα levels during treatment

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Abstract

Elevated tumor necrosis factor (TNF)-α levels are associated with poor prognosis in patients with multiple myeloma (MM). Enbrel is a TNF antagonist fusion protein consisting of the extracellular, ligand-binding domain of the human p75 TNF receptor linked to the Fc portion of human IgG1. Ten patients with refractory MM were treated with Enbrel 25 mg s.c twice weekly for a minimum of eight median age was 63 years (range, 43–76). The total number of Enbrel doses was 191 (median 16; range, 3–55). TNFα plasma levels increased significantly during treatment with Enbrel. No objective response occurred. Acceleration of disease occurred in four patients. While well-tolerated, Enbrel did not have anti-myeloma activity as administered on this study.

Keywords: Refractory; Multiple myeloma; TNFα; Enbrel

1. Introduction

The management of patients with relapsed or refractory multiple myeloma (MM) remains inadequate and novel treatment modalities are urgently needed. The response rate with standard therapy, including combination chemotherapy with vincristine, adriamycin, and dexamethasone (VAD) is approximately 60% [1–3]. Thalidomide single-agent therapy is associated with overall response rates of approximately 30% and 2 years overall and failure-free survival rates of 48 and 20%, respectively [4,5].

Among the potential MM growth factors, tumor necrosis factor (TNF)-α is a survival factor for MM cell lines, induces MM cells in the cell-cycle and promotes long-term growth of malignant plasma cells [6]. It promotes the growth of MM cell lines, sometimes in a synergistic manner with interleukin-6 (IL-6), but also may clearly act through a pathway independent of IL-6, having a growth-promoting effect at least equal to that of IL-6 [7–11]. TNFα is also a potent bone-resorbing factor and plays an important role in the development of the osteolytic bone lesions observed in MM patients [12–15]. In some models, the role of TNFα in MM is more complex; it stimulates both growth and apoptosis of some plasma cell lines and some ex-vivo plasma cells [8,16]. Fillela et al. found that TNFα serum levels were increased in 44% of patients with newly diagnosed MM and 50% of those with progressive disease [11]. TNFα serum levels were significantly higher in persons with monoclonal gammopathy of undetermined significance (MGUS), or patients with progressive MM compared with healthy subjects; patients with progressive MM also had significantly higher TNF levels than patients with stable MM. Furthermore, concentrations of TNFα are significantly higher in patients with bone disease than in those without overt lesions [17].

Two distinct receptors for TNF of 55 and 75 kDa have been identified [18,19]. A recombinant TNF receptor p75-Fc fusion protein (Enbrel, Immunex, Seattle) was developed targeting to neutralize TNF, reducing its biologic activity [20]. DNA encoding the Fc portion of a human immunoglobulin (Ig) G1 molecule was linked to DNA encoding the soluble portion of human p75 TNF receptor. The combined DNA was expressed in a mammalian cell line, resulting to an Ig-like dimer. This soluble TNFR-Fc fusion construct acts

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as a competitive inhibitor of TNF, preventing its binding to the cell surface TNF receptors; it also renders it biologically unavailable [20].

Studies in healthy normal volunteers and in patients with rheumatoid arthritis [21–24] Wegener's granulomatosis [25] and advanced heart failure have shown that Enbrel is safe [21–28]. However, in patients with established septic shock caused by Gram-positive organisms there was a non-significant trend toward increased rates of mortality in those treated with higher doses of Enbrel in comparison with the placebo group; a similar tendency to increased mortality rates was also noted with the use of an anti-TNF monoclonal antibody on a prior study in a similar patient population [29–31].

An effective anti-TNF agent might be of therapeutic benefit in patients with MM. As an initial investigation of the safety of Enbrel in this immunocompromised population, already prone to sepsis, we conducted a pilot study of Enbrel, as a single agent, in patients with advanced or refractory MM. Measurements of TNFα, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), and IL-6 were performed before and during treatment with Enbrel.

2. Materials and methods

2.1. Study group

Patients with refractory MM were entered onto the study between August and December 2000, after written informed consent was obtained according to institutional guidelines. Refractory MM was defined as: (a) primary resistant MM, progressive disease during receipt of at least two courses of induction chemotherapy, which includes an alkylating agent and/or a topoisomerase II inhibitor; (b) transient response; defined as response but relapse while still on induction therapy; or (c) relapsed disease, i.e. post-remission or -plateau relapse Eligibility criteria included patients with a quantifiable serum paraprotein or Bence-Jones proteinurea and a bone marrow plasmacytosis >5%, without overt infection, hypotension, concurrent chemotherapy, systemic radiotherapy, pregnancy or overt psychosis.

Pretreatment evaluation included history taking and physical examination; complete blood count, differential, and platelets count; serum chemistries, including liver and renal function studies; bone marrow aspiration with or without biopsy; β_2-M, serum immunoelectrophoresis, serum protein, immunoglobulin assay and M-band quantitation by immunofixation, 24 h urine collection for Bence-Jones protein, total protein, and creatinine; and radiologic assessment as indicated.

2.2. Measurement of cytokine levels

2.2.1. Plasma and serum collection

Plasma and serum samples were collected and stored according to approved protocols from eight patients on study who consented to provide these specimens for cytokine assay prior to first Enbrel therapy, at 2–3 week intervals while on study, and after completion of study therapy.

2.2.2. Enzyme-linked immunosorbent assay

The enzyme-linked immunosorbent assays (ELISAs) for TNFα, VEGF, bFGF, HGF, and IL-6 were performed using commercially available kits from R&D Systems (Minneapolis, MN). Manufacturer's recommended protocols were followed. Briefly, plasma was collected in tubes with EDTA and stored at −82 °C. Patient samples were added to separate microplates, each containing a specific monoclonal antibody and mixtures were incubated at room temperature for 2 h. The plates were washed three times to remove any unbound substances. Protein-specific enzyme-linked polyclonal antibodies were added to the wells. Subsequently, the mixtures were incubated at room temperature for 2 h followed by another washing to remove any unbound antibody or enzyme reagent. A substrate solution was added to the wells, and a blue color developed. The intensity of the blue was proportionate to the amount of cytokine bound in the initial step. The color development was stopped, and the intensity of the color was measured and compared with a standard curve. Reading was done at 450 nm wavelength for TNFα, VEGF, bFGF, HGF, and IL-6.

2.3. Therapy

Treatment consisted of Enbrel 25 mg twice weekly subcutaneously (s.c.) for a minimum of eight doses (4 weeks; one cycle). If patient developed toxicity of grade 3–4 (NCI toxicity criteria), Enbrel was held until resolution to at least grade 1. Supportive care, including transfusion of blood and blood products, antibiotics, and analgesics were administered as needed.

2.3.1. Course timing

Enbrel was given for one course of treatment (4 weeks); if patients responded or had no signs of progression they received 16 additional doses (two courses) of Enbrel without interruption, at the same dose. Further courses were given if patients continued to respond or not to progress.

2.4. Endpoints and statistical methods

Complete response (CR) was defined as disappearance of serum and urine M-protein on electrophoresis and immunofixation in two determinations at least 4 weeks apart, <5% plasma cells in the bone marrow, normalization of peripheral blood values or biochemical abnormalities assignable to MM, and resolution of all soft tissue plasmatocytomas.

Partial response (PR) was defined as ≥50% reduction of serum M-protein; ≥50% reduction in the urine M-protein if the baseline value was ≥1 g/24 h and <0.1 g/24 h if baseline value was 0.5–1 g/24 h; and ≥50% reduction of sum

of the products of the cross diameters of each measurable lesion. Disease progression was defined as ≥50% increase in the serum or urine M-protein above the lowest previous level, and appearance of new plasmatocytomas or increase by ≥50% of soft tissue plasmatocytomas. Failure to meet criteria for response or progression was categorized as stable disease.

Toxicity was graded on a scale of 0–5 using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 2.0 criteria [32].

3. Results

3.1. Study group

The clinical characteristics of the 10 patients are summarized in Table 1. Median age was 63 years (range, 43–76; 70%) were older than 60 years. Eight patients (80%) were male; one had a performance status (PS) of 2 (10%). Five patients had progressive and five stable/refractory MM.

Table 1
Patients' characteristics

Characteristic	$N = 10$	%
Age		
Median	63	
Range	43–76	
>60	7	70
Male	8	80
PS >1	1	10
High β_2M (>3 mg/l)	8	80
Immunoglobulin type		
IgG	7	70
IgA	3	30
IgG Kappa chain deposition disease	1	10
Marrow involvement	6	60
Prior regimens		
0–2	1	10
3–7	9	90
Hb <10 g/dl	4	40
WBC $<1 \times 10^9\,l^{-1}$	3	30
PLT $<100 \times 10^9\,l^{-1}$	2	20
M-protein >3 g/dl	5	50
Bone lesions		
0–2	3	30
>3	7	70
Karyotype		
Diploid	4/5	80
48–49, XY, −1, +add(3)(p26), −11, del(13)(q12q14), +14, −17 × 2, +19, −22, +4mar	1/5	20
Prior thalidomide	10	100
Prior hyper-CVAD	6	60
Prior allogeneic transplant	2	20

Median number of prior treatments was five (range, 2–7). All patients had received prior therapy with thalidomide, six had received fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) regimen, five had received high-dose melphalan, two had received stem cell transplant; two had received Biaxin, and two patients had received IFN-α. The maximum response to prior treatment was CR in one patient, PR in six patients, and SD in three patients. One patient had IgG Kappa chain deposition disease and Guillen-Barre like syndrome, six had IgG and three patients had IgA MM. Five patients had Stage I, two Stage II, and three Stage III disease as per the Durie and Salmon classification [33]. All patients with Stage I disease had received prior therapy for their disease based on symptoms attributable to their disease, usually fatigue and/or bone pain. Prior medical history was significant for recurrent severe infections in three patients: one had sinusitis, one urinary track infection due to β-hemolytic streptococcus, and one patient had bronchitis. The median Hgb value was 11 g/dl (range, 8.9–13.8); the median WBC $4.7 \times 10^9\,l^{-1}$ (range, 2.9–5.6) and the median platelet count was $199 \times 10^9\,l^{-1}$ (range, 57–356). The median M-protein was 2.7 g/dl (range, 0–4.7; M-protein was zero in a patient with Bence-Jones proteinuria, bone marrow infiltration, and >3 bone lytic lesions). Six patients had bone marrow infiltration. Two patients had 0–1 bone lesions, one patient 2, and seven patients had >3 bone lesions. The median creatinine was 1.0 mg/dl (range, 0.7–2.6), the median β_2-M 6.9 mg/l (range, 1.2–17.5) and the median serum calcium was 8.7 mg/dl (range, 7.7–10.5). Cytogenetic studies were successful in five patients; four had diploid karyotype and one patient had multiple chromosome abnormalities (48–49, XY, −1, +add (3)(p26), −11, del (13)(q12q14), +14, −17 × 2, +19, −2, +4mar).

3.2. Treatment results

Ten patients received a total of 25 cycles of Enbrel therapy. The median number of cycles administered was 2 (range, 1–7). The median number of doses was 16 (range, 3–55) and the total number of doses was 191.

3.2.1. Response

No patient had a complete or partial response to therapy. Four patients had progressive disease on study, including two patients who were withdrawn early (after 2 and 4 weeks; Table 2). Among the four patients who progressed, three patients had stable MM on study entry.

3.3. Cytokine levels

Cytokine plasma levels were measured in eight patients who agreed to provide samples before and during treatment with Enbrel (Table 3). TNFα plasma levels were significantly higher during Enbrel treatment compared with the levels before treatment. In contrast, there was no significant

Table 2
Response

Patients	MM status on entry	Duration of Rx (weeks)	M-protein baseline	M-protein min during Rx	M-protein (end of Rx)	M-protein increase (%)	Response
1	SD/refractory	12	0.10	0.20	0.20	50	PD
2	PD	8	3.70	4.30	4.80	30	SD[a]
3	PD	26	3.20	3.50	3.50	9	SD[b]
4	SD/refractory	4	1.30	2.20	2.20	69	PD
5	PD	2	0.13	0.42	0.56	460	PD[c]
6	SD/refractory	9	4.70	4.50	5.30	13	SD
7	SD/refractory	12	4.00	4.00	6.80	70	PD
8	PD	3	2.20	2.20	3.10	41	SD
9	PD	8	0.30	0.30	0.30	0	SD
10	SD/refractory	27	3.40	3.20	3.50	3	SD

[a] Improvement in Hgb from 9.7 to 10.4 g/dl, WBC (4.4–5.8) × 10^6 l^{-1}, bone marrow plasma cells reduced from 32 to 18%.
[b] Progressive growth of myeloma slowed.
[c] Early removal from the study.

Table 3
Cytokine levels in plasma of patients treated with Enbrel

Cytokine levels	Median (range)	Mean (±2S.D.)	*P*-value
TNFα			
Pretreatment	8.0 (6.7–9.1)	7.9 (±1.4)	0.006
During treatment	243.6 (72.7–413.9)	250.8 (±243.93)	
VEGF			
Pretreatment	77.7 (38.5–294.1)	118.3 (±196.7)	0.20
During treatment	68.3 (43.4–91.4)	64.6 (±39.4)	
Bfgf			
Pretreatment	20.4 (8.6–57.8)	25.4 (±38.0)	0.22
During treatment	17.2 (7.3–25.2)	16.0 (±16.3)	
HGF			
Pretreatment	786.3 (540.3–1527.5)	855.1 (±743.6)	0.63
During treatment	743.2 (371.8–2009.3)	898.3 (±1148.4)	
IL-6			
Pretreatment	2.7 (2.4–8.9)	3.89 (±7.7)	0.44
During treatment	3.4 (1.9–8.4)	4.08 (±5.6)	

difference before and during treatment with Enbrel in the plasma levels of VEGF, bFGF, HGF, and IL-6.

3.4. Toxicity

Enbrel was associated with grade 2 fever in two patients; grade 1 fatigue in one; grade 2 flu-like syndrome in two; grade 2 chest pain in one; grade 2 abdominal discomfort in one; and grade 1 hyperbilirubinemia in one. There were no overt allergic reactions to Enbrel. No patient was withdrawn from the study because of toxicity. There was no increased mortality rate in patients treated with Enbrel. No patients developed sepsis while on study.

4. Discussion and conclusion

The administration of Enbrel at the dose of 25 mg s.c. twice weekly was not associated with overt serious adverse events in these patients with heavily pretreated refractory MM. There was no evidence of cumulative toxicity, and the more common adverse events were fever and flu-like syndrome. More importantly, there was no increased mortality rate among patients treated with Enbrel. However, no responses were observed. Four patients progressed and six patients had stable disease.

The safety profile of Enbrel in patients with MM in our study is in line with other reports in patients with rheumatoid arthritis [21–24], Wegener's granulomatosis [25], and advanced heart failure, [27,28] showing that Enbrel is well-tolerated. The most common side effects, such as injection site reactions and upper respiratory tract infections, seen in other disorders, were not noted in our study population [34,35]. The stimulus to perform the currently reported pilot safety study was the observation of a trend toward increased mortality rates with higher doses of Enbrel compared with a placebo group in patients with documented sepsis from Gram-positive bacteria [29]. The same trend has been observed in two trials of an anti-TNFα monoclonal antibody for the treatment of sepsis: in non-shock patients receiving a 15 mg/kg dose in one study [30], and in shock patients treated with the same dose in a second study [31].

Enbrel is a dimer of the p80 TNF receptor linked by the Fc portion of IgG1, which binds TNFα and lymphotoxin, neutralizing their effects. This dimeric construct of Enbrel has a higher affinity for TNF than the monomeric forms of the receptor. Additionally, the Fc peptide gives a longer half-life to the molecule [20]. The primary mechanism of its action is by binding to the TNFα, rendering it biologically unavailable. Preclinical and clinical studies have shown that Enbrel does not cause rapid removal of TNF from the biologic fluids, but does prolong TNF's half-life [20,36]. Enbrel has been reported to act as a TNF "carrier" [21,36]. This "carrier" activity of Enbrel may explain the finding of significantly higher TNFα values in patients during treatment on this study compared with their respective pretreatment values. This observation is in agreement with the study of Eason et al., who showed similar effects in patients with OKT3-acute

clinical syndrome [36]. These investigators demonstrated that the high TNFα antigenic levels were associated with concomitant low or undetectable TNFα bioactivity; high levels of TNF receptors were also noted >13 days after the administration of Enbrel, indicating its long half-life [36].

Despite this data suggesting that the elevated TNFα levels associated with Enbrel use are not bioactive, some caution must be applied in accepting that this is always so. A noteworthy event on the current study was the acceleration of MM in four patients soon after commencing Enbrel therapy, three of whom had entered on study with an immediate prior history of stable disease. In this study, we focused on safety in terms of lack of overt adverse events—Enbrel was clearly "safe" from this perspective. However, its safety in terms of modulation of disease activity in patients with MM will require much more attention in other studies. The source of the elevated circulating TNFα in patients with MM receiving Enbrel is of interest. Serial quantitative RT-PCR analyses of mRNA expression for relevant cytokines in both myeloma and stromal cells would be of benefit in future studies.

Neben et al. have investigated the genetic polymorphism in the TNFα in patients with relapsed and refractory MM treated with thalidomide [37]. Eight patients with MM carrying the −238A allele had higher TNFα levels in peripheral blood, prolonged 12 months progression free survival and a trend towards longer overall survival compared with patients with the −238G allele [37]. Among patients with the −238G allele, only one patient had achieved a CR. These investigators suggest that regulatory polymorphisms of the TNFα gene can affect TNFα production and the response to thalidomide. Of particular interest is the fact that all patients in our study had previously failed thalidomide; although no studies for genetic polymorphism were performed, it is possible that patients who progressed may have been carriers of the −238G allele.

Enbrel is also being investigated in patients with other hematologic malignancies. In a cohort of seven patients with acute myelogenous leukemia (AML), a single s.c. 25 mg dose resulted to a reduction of apoptosis in three out of five evaluable patients and increase of proliferation in three out of five patients [38]. The drug was well-tolerated without any side effects. In six patients, the WBC count stabilized or decreased, but no patient achieved an objective response. In patients with myelodysplastic syndromes, the combination of Enbrel with thalidomide was well-tolerated, and produced significant hematologic improvement in 4 out of 18 patients who completed 16 weeks of therapy [39]. Five patients had stable disease and three had a major erythroid response. In a pilot study in patients with myelofibrosis with myeloid metaplasia, Enbrel relieved constitutional symptoms and was well-tolerated but no objective responses were documented [40]. In a Phase 2 study of Enbrel, in 26 patients with refractory myeloproliferative malignancies, the agent was very well-tolerated, but no patients had a clinically meaningful response to therapy [41].

In conclusion, Enbrel had an acceptable safety profile in patients with refractory MM. As a single agent it did not induce any remissions. This pilot study involved a small patient cohort and thus, its findings are not definitive. Longer-term follow-up of a larger patient cohort would be required to properly assess any relationship between the increased levels of plasma TNFα associated with Enbrel therapy and disease behavior in patients with MM.

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EXHIBIT 1

Continued from previous page

evaluable patients who were given the 27 mg/m² dose after the first cycle, Dr. Wang said.

The trial is ongoing at the higher dose, with a target accrual of 269 patients with relapsed and refractory myeloma and a goal of accelerated approval for carfilzomib, Dr. Siegel added.

Carfilzomib With Len/Dex

The phase IB PX-171-006 dose-escalation trial explored the hypothesis that adding carfilzomib to the Len/Dex regimen would result in activity superior to that previously achieved in relapsed and refractory patients who were given bortezomib with Len/Dex.

Dr. Ruben Niesvizky, clinical director of the multiple myeloma service at New York–Weill Cornell Medical Center, New York, reported on 32 patients (median age, 60 years) who had one to three prior treatments, including bortezomib in 72% and immunomodulatory agents in 87.5%.

Efficacy results on 29 patients showed an overall response rate of 59% (six CR or near CR, five VGPR, and six PR).

In addition, four patients had minimal responses and six had stable disease, bringing the disease control rate to 93%.

Not only was administration for more than 16 months possible, but responses improved with prolonged treatment, according to Dr. Niesvizky, also of New York–Weill Cornell Medical Center.

The trial is ongoing, with an expansion cohort of 30 patients to receive the higher carfilzomib dose and a full 25-mg lenalidomide dose, Dr. Niesvizky commented.

A randomized, multinational phase III trial is also opening in 2010 with a target accrual of 700 patients who have relapsed after one to three prior therapies. It will compare carfilzomib plus Len/Dex vs. Len/Dex alone. ■

Comment

Pomalidomide was among the promising new agents at the ASH meeting. Dr. Richardson and Dr. Lacy presented exciting data that this more potent immunomodulatory drug can achieve responses in relapsed and refractory myeloma that is refractory to lenalidomide and bortezomib. Moreover, the side effect profile shows that it is well tolerated.

Carfilzomib, the novel proteasome inhibitor, is another new drug of interest. The monotherapy trial presented by Dr. Wang and Dr. Siegel achieved response rates of 46% in patients with relapsed myeloma who have not had bortezomib, and 18% in those who have had bortezomib. The side effect profile was very favorable, with a very low rate of neuropathy. We eagerly await more data on the response rate in patients who have bortezomib-refractory myeloma, as well as data from Dr. Niesvizky on the combination of carfilzomib with lenalidomide and dexamethasone.

—Kenneth C. Anderson, M.D.

Pomalidomide Picks Up Where Both Earlier IMiDs Stop Working

BY JANE SALODOF MACNEIL

NEW ORLEANS — Pomalidomide, a novel third-generation immunomodulatory agent in early trials, is drawing responses in patients with relapsed and refractory multiple myeloma that has progressed when treated with its predecessors, lenalidomide and thalidomide.

"Structurally, it is very similar to lenalidomide and thalidomide, but small differences in structure mean very important differences in terms of side effect profile, efficacy, and potency," Dr. Martha Q. Lacy of the Mayo Clinic in Rochester, Minn., told attendees at the American Society of Hematology annual meeting.

Neutropenia should be more manageable in the next phase, as growth factor support will be allowed.

Dr. Richardson

"One can argue that it is perhaps the best of both," said Dr. Paul Richardson of the Dana-Farber Cancer Institute in Boston.

The two investigators presented slightly different trials but reported similar results, with response rates of 50% or better in heavily pretreated populations. Neutropenia was the leading side effect in both studies, and combination therapy with low-dose dexamethasone was active in patients who had stopped responding to that drug as well.

The studies followed an earlier trial for which Dr. Lacy and colleagues reported an overall response rate of 63% to pomalidomide plus dexamethasone in 60 patients who had relapsed after one to three prior myeloma regimens (J. Clin. Oncol. 2009;27:5008-14).

Monotherapy and Combination Tested

Dr. Richardson reported on the dose-finding portion of a phase I/II trial testing pomalidomide alone and in combination with dexamethasone. All 32 patients (mean age 67 years) in phase I had prior lenalidomide, bortezomib, and dexamethasone; 78% had prior thalidomide, and 59% had undergone stem cell transplant.

The full population started on pomalidomide monotherapy. Low-dose dexamethasone was later added at clinician discretion for 15 patients (47%) who did not respond or had disease progression.

All told, Dr. Richardson reported that one patient with a complete response (CR) was among 7 of 25 evaluable patients (28%) who had a partial response (PR) or better, and 13 (52%) who had at least a minimal response (MR).

In the group given combination therapy, response improved in 8 patients (53%) after dexamethasone was added; durability of response also increased from 13.5 to 16.9 weeks.

Investigators determined the maximum tolerated dose to be 4 mg daily on the first 21 days of 28-day cycles.

Grade 3/4 neutropenia was the dose-limiting toxicity, occurring in four patients at a 5-mg dose. Along with fatigue, neutropenia was the most common adverse event, occurring in almost a third of patients. One case of peripheral neuropathy and two cases of venous thromboembolism were observed.

VITALS

Major Finding: Investigational third-generation IMiD is active in patients who no longer respond to lenalidomide, thalidomide, or other agents for multiple myeloma.

Data Source: 65 patients in small phase I and II trials.

Disclosures: Celgene Corp. sponsored the studies. Dr. Richardson disclosed membership on advisory boards of Celgene, Millennium Pharmaceuticals Inc., and Johnson & Johnson. His coinvestigators included employees of Celgene. Dr. Lacy said she had no financial disclosures, but some coinvestigators said they had received honoraria from Celgene.

The only deaths in the study resulted from myeloma, Dr. Richardson said; none were treatment related.

The phase II portion of the trial is currently accruing toward a goal of 200 patients in 2010. The hope is that a robust response in a population this size could lead to accelerated approval of pomalidomide, Dr. Richardson said.

He also expressed optimism that neutropenia would prove less of a problem than in phase I, as the use of a growth factor was not permitted in the first part.

"Going forward in phase II, growth factor will be allowed, so we think this neutropenia will be manageable," he said.

Pomalidomide Plus Low-Dose Dexamethasone

Dr. Lacy reported on a new phase II trial of pomalidomide with low-dose dexamethasone in 34 resistant and refractory patients (median age 61.5 years) who were previously treated with lenalidomide.

This regimen started at 2 mg of pomalidomide daily throughout two 28-day cycles, along with daily aspirin (325 mg) and 40 mg of dexamethasone on days 1, 8, 15, and 21. After two cycles, the pomalidomide dose could be increased to 4 mg if patients had no response or progressed.

In addition to all patients having previous exposure to lenalidomide, 19 patients had prior thalidomide and 20 had prior bortezomib; 23 patients had had stem cell transplants.

At a mean follow-up of 6 months, 28 patients (82%) were still alive, with no progression seen in 16 patients. The confirmed response rate was 32%, including 1 CR and 10 very good partial responses. Another 6 patients had minimal responses, and 11 had stable disease.

Among the responders were five patients with previous exposure to thalidomide and six to bortezomib. Four of 14 high-risk patients had partial responses.

Dr. Lacy noted that the investigators were encouraged to see that progression-free survival and overall survival curves were similar for high-risk and standard-risk patients in early data from the trial.

Toxicity was manageable, she said, with the leading event being grade 3/4 neutropenia in nine patients.

No deep vein thrombosis was seen, and although eight patients had grade 1/2 neuropathy, it had been seen at baseline in five cases. ■

EXHIBIT 2

Access

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Original Article

Leukemia , (9 September 2010) | doi:10.1038/leu.2010.190

Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM)

M Q Lacy, S R Hayman, M A Gertz, K D Short, A Dispenzieri, S Kumar, P R Greipp, J A Lust, S J Russell, D Dingli, S Zeldenrust, R Fonseca, P L Bergsagel, V Roy, J R Mikhael, A K Stewart, K Laumann, J B Allred, S J Mandrekar, S V Rajkumar and F Buadi

Patients with multiple myeloma progressing on current therapies have limited treatment options. Pomalidomide (CC4047), an immunomodulatory drug, has significant activity in relapsed myeloma and previous studies suggest activity in lenalidomide refractory disease. To better define its efficacy in this group, we treated a cohort of lenalidomide refractory patients. Pomalidomide was given orally (2 mg) daily, continuously in 28-day cycles along with dexamethasone (40 mg) given weekly. Responses were assessed by the International Myeloma Working Group Criteria. Thirty-four patients were enrolled. The best response was very good partial response in 3 (9%), partial response (PR) in 8 (23%), best responses (MR) in 5 (15%), stable disease in 12 (35%) and progressive disease in 6 (18%), for an overall response rate of 47%. Of the 14 patients that were considered high risk, 8 (57%) had responses including 4 PR and 4 MR. The median time to response was 2 months and response duration was 9.1 months, respectively. The median overall survival was 13.9 months. Toxicity was primarily hematologic, with grade 3 or 4 toxicity seen in 18 patients (53%) consisting of anemia (12%), thrombocytopenia (9%) and neutropenia (26%). The combination of pomalidomide and dexamethasone (Pom/dex) is highly active and well tolerated in patients with lenalidomide-refractory myeloma.

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EXHIBIT 3

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Activity of pomalidomide plus dexamethasone (Pom/dex) in dual lenalidomide/bortezomib refractory multiple myeloma (MM).

Sub-category: Multiple Myeloma

Category: Lymphoma and Plasma Cell Disorders

Meeting: 2010 ASCO Annual Meeting

Citation: J Clin Oncol 28:7s, 2010 (suppl; abstr 8002)

Abstract No: 8002

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Author(s): M. Lacy, M. A. Gertz, S. R. Hayman, A. Dispenzieri, S. Kumar, J. Mikhael, A. K. Stewart, J. Allred, S. J. Mandrekar, S. V. Rajkumar; Mayo Clinic, Rochester, MN; Mayo Clinic, Scottsdale, AZ

Abstract:

Background: Patients with MM who have progressed after multiple novel agents have limited treatment options. Pomalidomide (CC4047) is the newest immunomodulatory (IMiD) agent. Pom/dex has demonstrated response rates (≥PR) of 63% in relapsed MM (JCO 2009, 27:5008-5014) and 32% in a lenalidomide-refractory cohort (ASH 2009). The efficacy of pomalidomide in patients who have failed both lenalidomide and bortezomib is unknown and this study was designed to study this question. **Methods:** Patients refractory to both lenalidomide and bortezomib therapy; defined as relapsing on or within 60 days of stopping each regimen, were enrolled. Pomalidomide was given orally 2 mg daily on days 1-28 of a 28-day cycle with oral dexamethasone given 40 mg daily on days 1, 8, 15 and 22. Response was assessed by the International Myeloma Working Group Uniform Response criteria. All patients received aspirin 325 mg daily for DVT prophylaxis. **Results:** 35 patients resistant/refractory to lenalidomide and bortezomib were enrolled. The median age was 62 years (range, 39-77). The median time from diagnosis to enrollment was 63 months (range 27-249). 14 patients had high risk molecular markers including loss of 17p (N=5), t(4;14) (N=4) and plasma cell labeling index ≥3% (N=8) The median number of prior regimens was 6 (3-9) including 81% with ≥5 prior regimens. Toxicity consisted primarily of myelosuppression: grade 3/4 neutropenia (29%); grade 3/4 thrombocytopenia (3%); and grade 3/4 anemia (9.6%). Grade 3/4 non-hematologic toxicities occurred in 16%: pneumonitis (3%), hyperglycemia (3%), renal failure (3%), fatigue(3%) thrombosis (3%). Grade 1 or 2 neuropathy occurred in 6% (3% grade 1; 3% grade 2). Best responses consist of VGPR 3 pts (9%), PR 8 pts (23%), and MR 5 pts (14%) (ORR 46%). With a median follow-up of 2.7 months, 77% remain progression free, and 94% remain alive. **Conclusions:** Pom/dex is active and well tolerated in this heavily pre-treated population of dual bortezomib/lenalidomide-refractory MM patients. The majority of patients have not progressed and objective responses are seen in 49%. This study confirms therapeutic benefit for Pom/dex in patients relapsing after other novel therapies.

Abstract Disclosures

Annual Meeting Planning Committee Disclosures

▸ Other Abstracts in this Sub-Category: